Digoxin, hypercalcaemia, and cardiac conduction

Adrian Vella, Thomas C Gerber, David L Hayes, Guy S Reeder

Summary

The cardiac effects of hypercalcaemia are usually manifest as a shortening of the QT-interval. Hypercalcaemia is infrequently associated with a clinically manifest arrhythmia. However, concomitant therapy with digoxin or underlying cardiac disease can potentiate the arrhythmogenic effects of hypercalcaemia, leading to a symptomatic rhythm disorder. We describe a symptomatic arrhythmia, which developed in a patient with hypercalcaemia secondary to squamous cell carcinoma of the bronchus. The patient was on digoxin therapy at the time. The arrhythmia did not recur after discontinuation of digoxin therapy and correction of the hypercalcaemia. Because of its effect on cardiac conduction, hypercalcaemia should be considered in the evaluation of any patient with an unexplained bradyarrhythmia. Conversely, patients with hypercalcaemia should discontinue digoxin therapy and be evaluated for the presence of rhythm disorders while receiving appropriate treatment for hypercalcaemia.

Keywords: hypercalcaemia; bradycardia; cardiac conduction; arrhythmia

Clinical observations of conduction disturbances caused by hypercalcaemia are rare. A few case reports exist describing patients with bradyarrhythmias such as atrioventricular (AV) nodal conduction defects, sinus node dysfunction and atrial fibrillation in the setting of hypercalcaemia. Underlying disease of the conduction system or cardiomyopathy may play a role in the pathogenesis of the observed arrhythmias.[1 2] We describe a patient with hypercalcaemia due to malignancy who developed a symptomatic bradyarrhythmia while on digoxin therapy and review the literature.

Case report

An 81-year-old woman had a sudden syncopal episode without premonitory symptoms while having a meal. She regained consciousness within one minute. Bystanders noted a slow radial pulse and a flushed complexion. She was admitted to a local hospital for evaluation and continuous cardiac monitoring.

Over the year preceding admission, she had been evaluated repeatedly by her local physician for weakness, dyspnoea and malaise associated with an unexplained 4.5 kg weight loss. A presumptive diagnosis of congestive heart failure was made and since that time, the patient had been treated with digoxin and loop diuretics. Over the 8 weeks prior to admission, she developed a cough productive of green sputum.

During the 12 hours following admission, the patient had several sinus pauses of 2.0 to 5.1 seconds. Laboratory evaluation on admission was remarkable for a total calcium of 3.0 mmol/l (normal 2.2–2.5). The serum digoxin level was 1.5 ng/ml (0.5–2.0). The chest X-ray showed a left upper lobe infiltrate of indeterminate nature but was otherwise unremarkable with no signs of congestive heart failure or pulmonary venous hypertension. The patient was transferred to our facility for further evaluation and treatment.

Physical examination revealed an elderly woman in no apparent distress. There was no palpable lymphadenopathy. Her pulse was regular in rate and rhythm at 74 beats/minute. There were no added heart sounds and examination of her chest and abdomen was unremarkable. She was oriented to time, place and person and there were no focal neurological deficits.

A 12-lead electrocardiogram (ECG) obtained on admission was notable for the presence of first-degree AV block. Temporary transvenous pacing was established. The hypercalcaemia resolved after intravenous hydration and diuretic therapy. Subsequently, no further sinus pauses were observed. A computed tomography scan of the thorax revealed an ill-defined, peripheral, bronchocentric lesion in the left upper lobe. Mediastinal and hilar adenopathy was also present. Transthoracic echocardiography showed a normal ejection fraction of 55%. There were no regional wall motion abnormalities. The serum parathyroid hormone was appropriately suppressed at 0.8 pmol/l (1.0–5.2). Bronchoscopy revealed an endobronchial lesion in the right main bronchus that was biopsied. The histology showed Grade 3 squamous cell carcinoma. An oncology consultation was obtained and after explanation of the therapeutic options, the patient elected not to pursue chemotherapy or radiotherapy.

Since the patient declined therapy for her malignancy, she was felt to be at risk for recurrent bradyarrhythmias and a permanent pacemaker was placed to prevent further symptoms. Digoxin was discontinued and she was discharged home after uneventful pacemaker placement. First degree AV block was still present on the ECG obtained on dismissal. Serum calcium levels were normal at that time.

Department of Internal Medicine, Mayo Clinic & Foundation, 200 First Street SW, Rochester, MN 55905, USA
Division of Endocrinology
A Vella
Division of Cardiology
T C Gerber
D L Hayes
G S Reeder

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Discussion

CARDIAC CONDUCTION AND HYPERCALCAEMIA

Within the range of calcium concentrations that are compatible with life, Ca^{2+} has little effect on the resting membrane potential. However, phase 2 of the action potential, the total duration of the action potential, and the duration of the effective refractory period tend to be prolonged by hypocalcaemia and shortened by hypercalcaemia.[3 4]

Hypercalcaemia has been shown to decrease cardiac conduction velocity and shorten the refractory time. This facilitates re-entry mechanisms and the development of complex ventricular arrhythmias. The main ECG manifestation of hypercalcaemia is a shortened QT-interval, sometimes associated with a slight prolongation of the PR and QRS-intervals. In patients with severe hypercalcaemia (>3.4 mmol/l), second or third degree AV block can occur.[3–5] The prolongation of the QTc seen in patients with hypocalcaemia is associated with a prolongation of the ventricular refractory period which may have an anti-arrhythmic action. The reverse is true of the shortened ventricular refractory period seen in hypercalcaemia (box 1). Vagal activity could play a role in the production of arrhythmia because atropine abolishes the arrhythmias created by the infusion of calcium-containing solutions.[6]

Sudden death in patients with hypercalcaemia has been reported. The proposed mechanism of death in these patients is ventricular fibrillation secondary to the underlying electrolyte disturbance.[7–9] In a retrospective review of 47 patients with conservatively managed hyperparathyroidism, Corlew *et al* identified one patient whose death was attributable to a malignant ventricular arrhythmia.[10] Rosenqvist *et al* studied cardiac conduction in 20 patients with hypercalcaemia caused by primary hyperparathyroidism.[11] These patients had no clinical, radiological or ECG evidence of underlying heart disease and underwent continuous ECG monitoring in the presence of hypercalcaemia before surgery and after normalisation of serum calcium values in the postoperative period. In this series there was no difference in the prevalence of supraventricular or ventricular arrhythmias. No high-grade AV-block was observed. A postoperative prolongation of the QTc was noted in all patients.[11]

A review of the records of 193 patients with surgically treated primary hyperparathyroidism identified two patients with a junctional rhythm prior to surgery. No ventricular arrhythmias were noted in this series.[12] Continuous 24-hour ECG monitoring undertaken in eight patients with hypercalcaemia (2.9–4.4 mmol/l) due to metastatic breast cancer did not detect any significant arrhythmias. Extrasystoles seemed to occur more frequently in these patients than in the general population. The frequency of ventricular ectopy did not change with the correction of hypercalcaemia and was attributed to the toxic effects of the anthracycline-based chemotherapy that all of these patients received.[2]

Effects of ↑Ca^{2+} on cardiac conduction

- lowering of the excitation threshold
- shortening of phase 2 of the action potential
- shortening of the effective refractory period
- decreased myocardial conduction velocity
- facilitation of re-entry
- shortened QTc
- second or third-degree AV block with Ca^{2+} >14.0 mmol/l

Box 1

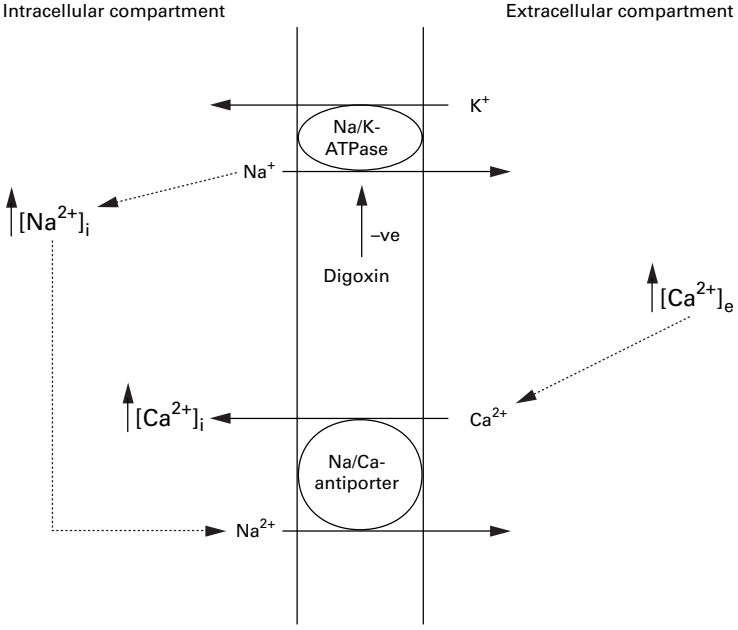

Figure Digoxin increases intramyocardial levels of calcium by indirectly increasing the activity of the sodium/calcium antiporter; $[Ca^{2+}]_i$ = intracellular calcium and $[Ca^{2+}]_e$ = extracellular calcium

DIGOXIN AND HYPERCALCAEMIA

The interaction between hypercalcaemia and digoxin is often overlooked. Cardiac glycosides potentiate the effect of hypercalcaemia on cardiac conduction. Digoxin and the other glycosides inhibit the myocardial Na^+/K^+-ATPase, thereby increasing intracellular sodium which, in turn, inhibits the Ca^{2+}/Na^+-antiporter and increases intracellular calcium levels (figure).[3] Both digoxin and hypercalcaemia decrease the excitation threshold and shorten the effective refractory period in the ventricles and have similar effects on the automaticity of ectopic pacemakers (box 2). Symptoms and signs of digoxin toxicity may appear at normal digoxin levels in the presence of hypercalcaemia.[3–5 13]

Discussion

The patient described in this article developed a symptomatic bradyarrhythmia in the setting of hypercalcaemia and concomitant digoxin use. Other than first degree AV block, there was no other clinical or echocardiographic evidence of underlying heart disease. Since the brady-

Effects of digoxin on cardiac conduction

- lowering of the excitation threshold*
- shortening of the effective refractory period*
- increased atrioventricular refractoriness*

*Potentiates the effect of hypercalcaemia

Box 2

arrhythmia was temporally related to the development of hypercalcaemia, but resolved after normalisation of the serum calcium, we conclude that the symptomatic sinus pauses in this patient were due to the combined effects of hypercalcaemia and digoxin on cardiac conduction. The resolution of the bradyarrhythmia was not related to discontinuation of digoxin. The patient took this medication on the morning of admission; therapeutic levels were present long after the cessation of bradyarrhythmia.

Although hypercalcaemia is commonly encountered clinically, bradycardia is infrequently observed in this setting. It is likely that there is significant inter-individual variability in the propensity to develop a cardiac conduction disturbance related to hypercalcaemia.

Hypercalcaemia can have many aetiologies. Some of these aetiologies have myocardial effects other than those mediated by hypercalcaemia. The possible causes of hypercalcaemia and potential cardiac effects other than those mediated by the hypercalcaemia are listed in box 3. Cardiac disease, or the underlying cause of hypercalcaemia, may increase the patient's susceptibility to the arrhythmogenic effects of hypercalcaemia.

Causes of hypercalcaemia and potential cardiac effects other than those mediated by hypercalcaemia

- thyrotoxicosis: thyrotoxic cardiomyopathy, increased myocardial irritability, tachycardia, atrial fibrillation (increased sensitivity to circulating catecholamines)
- phaeochromocytoma: increased myocardial irritability, tachycardia, atrial fibrillation (increased circulating catecholamines)
- Addisonian crisis:effects of $\uparrow K^+$, volume depletion
- theophylline intoxication: increased myocardial irritability
- sarcoidosis: infiltrative cardiomyopathy; destruction of the conducting system
- tuberculosis: constrictive pericarditis
- malignancy: effects of anthracycline chemotherapy; malignant pericardial effusion
- Paget's disease of bone: high output cardiac failure

Box 3

1 Kurnick JE, Hartman CR, Floyd GD, Spicer MJ, Nelson WP. Wenckebach phenomenon in thyrotoxicosis with hypercalcaemia. *Rocky Mountain Med J* 1973;**70**(10):46–7.
2 Lazzari R, Pellizzari F, Brusaferri A, Caobelli A. Ipercalcemia ed alterazioni del ritmo cardiaco [Hypercalcaemia and alterations of cardiac rhythm]. *Minerva Med* 1991;**82**: 255–7.
3 Surackwicz B. The interrelationship of electrolyte abnormalities and arrhythmias In: Mandel WJ, ed,*Cardiac arrhythmias. Their mechanisms, diagnosis & management.* Philadelphia: JPLippincott, 1995; pp 89–108.
4 Commerford PJ, Lloyd EA. Arrhythmias in patients with drug toxicity, electrolyte and endocrine disturbances. *Med Clin North Am* 1984;**68**:1051–78.
5 Carpenter C, May ME. Cardiotoxic calcemia. *Am J Med Sci* 1994;**307**:43–4.
6 Littledike ET, Glazier D, Cook HM. Electrocardiographic changes after induced Hypercalcaemia and hypocalcemia in cattle: reversal of the induced arrhythmia with atropine. *Am J Vet Res* 1976;**37**:383–8.
7 Surakwicz B. Role of electrolytes in etiology and management of cardiac arrhythmias. *Progr Cardiovasc Dis* 1966;**8**: 364–86.
8 Young JH, Emerson K. Parathyroid carcinoma associated with acute parathyroid intoxication. *Ann Intern Med* 1949;**30**:823.
9 Naik BK, Sarma RN, Copahao V, Pargaonker PS, Gopal P. Acute hyperparathyroidism. *Arch Intern Med* 1963;**111**:729.
10 Corlew DS, Bryda SL, Bradley EL, DiGirolamo M. Observations on the course of untreated primary hyperparathyroidism. *Surgery* 1985;**98**:1064–71.
11 Rosenqvist M, Nordenstrom J, Andersson M, Edhag OK. Cardiac conduction in patients with hypercalcaemia due to primary hyperparathyroidism. *Clin Endocrinol* 1992;**37**:29–33.
12 Gunst MA, Drop LJ. Chronic hypercalcaemia secondary to hyperparathyroidism: a risk factor during anaesthesia? *Br J Anaesth* 1980;**52**:507–11.
13 Voss DM, Drake EH. Cardiac manifestations of hyperparathyroidism, with presentation of a previously unreported arrhythmia. *Am Heart J* 1967;**73**:235–9.